We focus on the molecular pathophysiology of pancreatic ductal adenocarcinoma (PDAC) and urothelial bladder carcinoma (UBC) with a disease-oriented approach. We use patient samples, cultured cells, and genetically modified mice, giving a similar weight to the 3 model systems. Observations made at either of these levels are then extended through additional work. To translate the findings, we bring this knowledge to a “population” level – leveraging on information and samples from large patient cohorts – in close collaboration with Núria Malats’ Group (CNIO).

In PDAC, a main hypothesis is that cell differentiation is a potent tumour suppressor mechanism acting early in carcinogenesis. We use the excellent genetic mouse models available because these processes cannot be readily studied in humans. In mice, PDAC can originate in pancreatic progenitors and in adult acinar and ductal cells. Understanding the contribution of early molecular events is crucial to design better strategies for prevention and early tumour detection.

In UBC, we focus on identifying new genes, using them for improved tumour taxonomy, characterising the mechanisms of action, and applying this knowledge for improved prediction of outcome and therapy.

OVERVIEW

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RESEARCH HIGHLIGHTS

Pancreatic cancer molecular pathophysiology

The genetic/genomic changes associated with PDAC have been extensively described by the genome consortia, and there is increasing interest in defining the molecular changes that precede tumour development. Our lab has pioneered the notion that cell differentiation is the first tumour suppressor mechanism in the pancreas. Focusing on acinar cells, we have identified several novel transcriptional regulators involved – including GATA6, GATA4, NRS2, HNF1A, and NFIC. Dysregulation of these genes is associated with a scenario of pre-inflammation or inflammation, dependent on a functional interaction with the microbiome: antibiotic administration to deplete gut bacteria enhances the activity of the acinar programme and rescues the inflammatory predisposition of Nr5a2 heterozygous mice, with lesser effects on wild type mice. The relevance of these findings to PDAC development are being analysed. These studies provide the basis for the pharmacological and genetic manipulation of acinar differentiation as a tumour preventative strategy.

GATA6 is a master regulator of the “classical” PDAC transcriptional programme and its loss is associated with poor patient outcome. In mice, GATA6 loss promotes metastasis and immune evasion (with P. Martinelli). GATA4 loss also favours PDAC development/progression in mice. However, these proteins play opposite roles in inflammation and they contribute differently to tumour initiation. In collaboration with an international consortium, we have shown that tumours that lose both GATA6 and GATA4 have the worst outcome and we are assessing the hypothesis that GATA6 amplifications are associated with long-term survivorship, possibly by locking cells in a differentiated state. We are focusing on deciphering their overlapping and unique transcriptional programmes using a combination of mouse models and genomic approaches (i.e., RNA-Seq and ChIP-Seq).

New conditional knockout mouse models of Hnf1a, developed with J. Ferrer (CRG, Barcelona) and Sagrario Ortega (CNIO), show that HNF1A can act as a tumour suppressor in PDAC initiation. Using a dual recombinase system, we are assessing the role of HNF1A and its partner NRS2 in tumour maintenance.
The activity of these transcription factors is intertwined, and our overarching goal is to establish the rules and hierarchies governing the control of acinar differentiation and their contribution to preneoplasia and cancer.

Urothelial bladder cancer (UBC) genetics, biology, and clinical translation

We focus on understanding new UBC tumour suppressor genes that we identified through exome sequencing. STAG2 and RBM10. STAG2 codes for a cohesion subunit and RBM10 (with S. Martin Puig, CNIC). In contrast, RBM10 knockout urothelial organoids display partial growth factor independence, pointing to a role of RBM10 in the regulation of EGFR pathway activity.

Our translational studies focus on the prediction of response to cisplatin-based chemotherapy and to immune checkpoint blockade (ICB). In collaboration with Núria Malats and Spanish uro-oncologists, we are assessing the value of assessment signatures to stratify patients to receive more appropriate therapies (cisplatin-based chemotherapy vs ICB) in a randomised clinical trial.